

## Coeliac disease

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G R Corazza, V Villanacci

## Some considerations on the histological diagnosis

Coeliac disease (CD) is a gluten dependent enteropathy with a very high prevalence<sup>1</sup> and an increased mortality rate.<sup>2</sup> Our knowledge regarding the clinical and pathogenetic aspects of CD has increased considerably over the past few years, but its diagnosis today—like several decades ago—is still based on the biopsy confirmed presence of duodenal–jejunal mucosal lesions that improve after a gluten free diet.

Although the greatest diagnostic challenge in CD concerns the identification of patients to be subjected to intestinal biopsy, rather than the choice of histopathological criteria, it is believed that the currently used criteria<sup>3</sup> are often the source of disagreement between pathologists and clinicians and, at times, of misdiagnosis for the patients.

Based on the dynamic development pattern of coeliac lesions and on the frequent finding of cases of CD with mild lesions, Marsh<sup>3</sup> proposed a four stage grading, namely: (1) type 1 infiltrative lesions, characterised by normal mucosal architecture with an increased number of intraepithelial lymphocytes (IELs); (2) type 2 hyperplastic lesions, characterised by an increase in crypt depth without villous flattening; (3) type 3 destructive lesions, characterised by villous atrophy and crypt hypertrophy; and (4) type 4 hypoplastic lesions, characterised by villous atrophy with normal crypt height and IEL count. Oberhuber and colleagues<sup>4</sup> subsequently proposed a new standardised report scheme, based on the Marsh classification, in which stage 3 was split further into 3a, 3b, and 3c, characterised by mild villous flattening, marked villous flattening, and completely flat mucosa, respectively. At present, the Marsh classification of intestinal coeliac lesions, as modified by Oberhuber *et al*, is used by most pathologists to evaluate the intestinal lesions of patients with CD, both for diagnosis and to assess the regression of the lesions after a gluten free diet.

There is no doubt about the efficacy of the Marsh–Oberhuber grading system. It is more than conceivable that, considering the broad spectrum of lesions possibly present in CD and reflecting

their pattern of progression, it is valid under optimal clinical conditions. Nevertheless, we are concerned about the preservation of this validity in day to day clinical practice and with respect to the individual patient; that is, we are worried about its effectiveness and efficiency under these circumstances. An analysis based on many years of clinical experience reveals a series of theoretical and above all practical problems. As far as the first are concerned, it is known that the greater the number of diagnostic categories of a method the lower the interobserver and intraobserver agreement, with a consequent reduction in its diagnostic reproducibility.<sup>5</sup> This reduction, in turn, reflects indirectly, but to a considerable extent, on the accuracy of any diagnostic method. Although it is true that a highly reproducible method or criterion is not necessarily accurate, it is also true that a non-reproducible method or criterion cannot be accurate. Therefore, a simpler grading system would be expected to minimise any disagreement between pathologists and to facilitate the comparison between serial biopsy specimens in the follow up of treated patients.

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On a more practical level, the correct emphasis attributed by the Marsh–Oberhuber system to milder lesions of classic villous atrophy (stages 1, 2, 3a, and 3b) underlines the absolute need to pay great attention to a series of simple measures for the correct handling and processing of biopsy specimens. At least four endoscopic biopsies must be taken<sup>6</sup> and the specimens properly oriented and sectioned.<sup>7</sup> It is common knowledge that the tangential artefact that simulates shortness of the villi and increased round cell contents within the epithelium and lamina propria<sup>8</sup> can lead to an incorrect diagnosis of CD or even of refractory sprue.<sup>9</sup>

How can the Marsh–Oberhuber classification be simplified to improve its reproducibility without reducing its diagnostic accuracy with respect to CD? Obviously, type 1 infiltrative lesions (raised IEL count with normal duodenal villous architecture) cannot be put aside. These lesions are sometimes the only evidence of a gluten sensitive enteropathy in dermatitis herpetiformis<sup>10</sup> and are a sensitive, although not specific, marker of latent CD.<sup>11</sup> However, one problem is that Marsh does not define raised IELs counts,<sup>3</sup> and Oberhuber and colleagues<sup>4</sup> indicate that 40 IELs/100 epithelial cells should be the cutoff point, a figure derived from jejunal biopsies taken over 30 years ago. More recently, the upper limit of the normal range has been established as 25 IELs/100 epithelial cells,<sup>12</sup> and we therefore feel that IEL counts above this figure allow the diagnosis of a type 1 infiltrative lesion, and that IEL counts after CD3 staining must be reserved for patients without those villous abnormalities already indicating that they should be included in stages of greater histological severity. With regard to type 2 hyperplastic lesions, although we agree that they clearly represent a distinctive stage in the immunopathological spectrum of coeliac intestinal mucosa,<sup>3</sup> we doubt the usefulness of this category both in the diagnosis of new patients—who would, in any case, already be identified by the increased IELs—and in assessing the histological improvement after gluten withdrawal, because a clear transition from villous atrophy to isolated crypt hypertrophy has never been demonstrated after treatment. With regard to subtypes 3a and 3b proposed by Oberhuber *et al*,<sup>4</sup> characterised by mild and pronounced villous flattening, but not yet by flat mucosa, we suggest that they should be grouped into a single stage. In fact, it has been shown that the recognition of lesser degrees of villous atrophy leads to considerable interobserver and intraobserver variation,<sup>13</sup> which increases even further in the case of two diagnostic categories. With regard to type 3c lesions (classic villous atrophy with

**Table 1** The histological diagnosis of coeliac disease

Marsh–Oberhuber classification	Proposed classification
Type 1 Type 2 } →	Grade A
Type 3a Type 3b } →	Grade B1
Type 3c } →	Grade B2
Type 4 } →	Deleted

crypt hypertrophy), these are the most frequently seen lesion in CD and there is no doubt that this stage should be maintained. In contrast, Marsh's type 4 hypoplastic lesion (the irreversible extreme end of the gluten sensitive spectrum) has been made obsolete by the recent finding that refractory sprue, ulcerative jejuno-ileitis, and enteropathy type intestinal T cell lymphoma are characterised by an aberrant clonal IEL population.<sup>14</sup> The histochemical and molecular demonstration of this finding defines these complicated forms of CD with much greater certainty than the presence of type 4 hypoplastic lesions.

"We believe that a simplification of the current histological classifications of CD is necessary to make the work of pathologists more uniform and to facilitate the relationship between pathologists and clinicians"

In conclusion, we believe that a simplification of the current histological classifications of CD is necessary to make the work of pathologists more uniform and to facilitate the relationship between pathologists and clinicians. Therefore, we propose that the lesions characterising CD should be divided into non-atrophic (grade A) and atrophic (grade B), and that grade B lesions should be split into grade B1, in which the villous to crypt ratio is less than 3 : 1,<sup>15</sup> with still detectable villi, and grade B2, in which the villi are no longer detectable. Grade A lesions are characterised by the isolated increase

of IELs, better recognised with the aid of immunohistochemical techniques. Table 1 shows how the two classification systems compare with each other.

Obviously, controlled and prospective studies are needed to determine whether this classification has greater reproducibility and no decrease in accuracy compared with the Marsh-Oberhuber system, and whether it will be useful in the follow up of histological improvement after gluten withdrawal. However, within the framework of a scientific and non-clinical setting, which requires a more precise and detailed quantification of the intestinal lesions, we believe this proposed grading system is inappropriate and suggest the use of standardised morphometric techniques.<sup>16</sup>

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#### REFERENCES

- 1 **Maki M**, Mustalahti K, Kokkonen J, *et al*. Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003;**348**:2517–24.
- 2 **Corrao G**, Corazza GR, Bagnardi V, *et al*. Mortality in patients with coeliac disease and their relatives: a cohort study. *Lancet* 2001;**358**:356–61.
- 3 **Marsh MN**. Gluten, major histocompatibility complex and the small intestine. A molecular and

immunobiologic approach to the spectrum of gluten sensitivity (celiac sprue). *Gastroenterology* 1992;**102**:330–54.

- 4 **Oberhuber G**, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol* 1999;**11**:1185–94.
- 5 **Weile B**, Fischer Hansen B, Hagerstrand I, *et al*. Interobserver variation in diagnosing coeliac disease. A joint study by Danish and Swedish pathologists. *APMIS* 2000;**108**:380–4.
- 6 **Mee AS**, Burke M, Vallon AG, *et al*. Small bowel biopsy for malabsorption: comparison of the diagnostic adequacy of endoscopic forceps and capsule biopsy specimens. *BMJ* 1985;**291**:769–72.
- 7 **Rubin CE**, Brandborg LL, Phelps P, *et al*. Studies of celiac disease. I. The apparent identical and specific nature of the duodenal and proximal jejunal lesion in celiac disease and idiopathic sprue. *Gastroenterology* 1960;**38**:28–49.
- 8 **Perera DR**, Weinstein WM, Rubin CE. Small intestinal biopsy. *Hum Pathol* 1975;**6**:157–217.
- 9 **Shidrawi RG**, Przemioslo R, Davies DR, *et al*. Pitfalls in diagnosing coeliac disease. *J Clin Pathol* 1994;**47**:693–4.
- 10 **Fry L**, Seah PP, Harper PG, *et al*. The small intestine in dermatitis herpetiformis. *J Clin Pathol* 1974;**27**:817–24.
- 11 **Mahadeva S**, Wyatt JL, Howdle PD. Is a raised intraepithelial lymphocyte count with normal duodenal villous architecture clinically relevant? *J Clin Pathol* 2002;**55**:424–8.
- 12 **Hayat M**, Cairns A, Dixon MF, *et al*. Quantitation of intraepithelial lymphocytes in human duodenum: what is normal? *J Clin Pathol* 2002;**55**:393–5.
- 13 **Corazza GR**, Bonvicini F, Frazzoni M, *et al*. Observer variation in assessment of jejunal biopsy specimens. A comparison between subjective criteria and morphometric measurement. *Gastroenterology* 1982;**83**:1217–22.
- 14 **Cellier C**, Patey N, Mauvieux L, *et al*. Abnormal intestinal intraepithelial lymphocytes in refractory sprue. *Gastroenterology* 1998;**114**:471–81.
- 15 **Segal HG**, Petras RE. Small intestine. In: Sternberg SS, ed. *Histology for pathologists*. Lippincott-Raven, 1997:495–518.
- 16 **Corazza GR**, Frazzoni M, Dixon MF, *et al*. Quantitative assessment of the mucosal architecture of jejunal biopsy specimens: a comparison between linear measurement, stereology, and computer aided microscopy. *J Clin Pathol* 1985;**38**:765–70.